7 Feb 1987 Planning Commin

Keith Meehan
John Anders
Dave Wilson
Norman Edwards
Lorin Allred
Joe VanWag

18th Feb

Hearing on

ROCHE®

Wallsburg Estates

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.
Elderly Patients: In elderly and debilitated patients it is recommended that dosage be limited to the smallest effective amount to preclude the development of ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Adverse reactions to Limbitrol are those associated with the use of either component alone. Most frequently reported were drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Other side effects occurring less commonly included vivid dreams, impotence, tremor, confusion and nasal congestion. Many symptoms common to the depressive state, such as anorexia, fatigue, weakness, restlessness and lethargy, have been reported as side effects of treatment with both Limbitrol and amitriptyline.
Granulocytopenia, jaundice and hepatic dysfunction of uncertain etiology have also been observed rarely with Limbitrol. When treatment with Limbitrol is prolonged, periodic blood counts and liver function tests are advisable.
Note: Included in the listing which follows are adverse reactions which have not been reported with Limbitrol. However, they are included because they have been reported during therapy with one or both of the components or closely related drugs.
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

should deviations occur.
The intramuscular or slow intravenous administration of 1 to 3 mg in adults (or 0.5 mg in children) of physostigmine salicylate (Antilirium)[1-3] has been reported to reverse the manifestations of amitriptyline overdosage. Because of its relatively short half-life, additional doses may be needed at intervals of 30 minutes to 2 hours.
Convulsions may be treated by the use of an inhalation anesthetic rather than the use of barbiturates. Cardiac monitoring is advisable, and the cautious use of digitalis or other antiarrhythmic agents should be considered if serious cardiovascular abnormalities occur. Serum potassium levels should be monitored and kept within normal limits by the use of appropriate I.V. fluids. Standard measures including oxygen, I.V. fluids, plasma expanders and corticosteroids may be used to control circulatory shock.
Dialysis is unlikely to be of value, as it has not proven useful in overdosages of either amitriptyline or chlordiazepoxide.
Since many suicidal attempts involve multiple drugs including barbiturates, the possibility of dialysis being beneficial for removal of other drugs should not be overlooked.
Treatment should be continued for at least 48 hours, along with cardiac monitoring in patients who do not respond to therapy promptly. Since relapses are frequent, patients should be hospitalized until their conditions remain stable without physostigmine for at least 24 hours.
Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase.

References:

1. Granacher RP, Baldessarini RJ: Physostigmine: Its use in acute anticholinergic syndrome with antidepressant and antiparkinson drugs. *Arch Gen Psychiatry 32:*375-380, Mar 1975.
2. Burks JS, Walker JE, Rumack BH, Ott JE: Tricyclic antidepressant poisoning: Reversal of coma, choreoathetosis, and myoclonus by physostigmine. *JAMA 230:* 1405-1407, Dec 9, 1974.
3. Snyder BD, Blonde L, McWhirter WR: Reversal of amitriptyline intoxication by physostigmine. *JAMA 230:* 1433-1434, Dec 9, 1974.

Dosage and Administration: Optimum dosage varies with the severity of the symptoms and the response of the individual patient. When a satisfactory response is obtained, dosage should be reduced to the smallest amount needed to maintain the remission. The larger portion of the total daily dose may be taken at bedtime. In some patients, a